Chapter 1

Asymmetric Organocatalysis: New Modes of Chemical Activation

Introduction

The chemical substances that make up living organisms are predominantly chiral and often exist as single enantiomers in the body. For example, mammalian proteins are composed exclusively of L-amino acids and carbohydrates of D-sugars. Mammals are unable to metabolize the L-enantiomer of sugars except via intestinal bacteria, which has made the sugars prospects for reduced-calorie substitutes.[1] Intestinal bacteria are incapable of L-glucose metabolism, which results in the sugar's powerful laxative qualities.[2] Enzymes and receptors that control biological pathways are highly substrate specific and often will not recognize stereoisomers of their targets. During the early years of pharmaceutical development, the importance of this biological phenomenon was not appreciated and due to the lack of methods for generating pure stereocenters, pharmaceuticals were produced and tested only in racemic forms. However, racemic drug formulations contain a 50-50 mixture of two similar, yet distinct compounds that often act very differently within the body, the tragic consequences of thalidomide being the most infamous example. Thalidomide was prescribed to pregnant mothers as an anti-emetic for morning sickness between 1957 and 1961 and caused well over 10,000 cases

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[1] Livesey, G.; Brown, J. C. *J. Nutr.* **1995**, *125*, 3020.

[2] Raymer, G. S.; Hartman, D. E.; Rowe, W. A.; Werkman, R. F.; Koch, K. L. *Gastrointest. Endosc.* **2003**, *58*, 30.

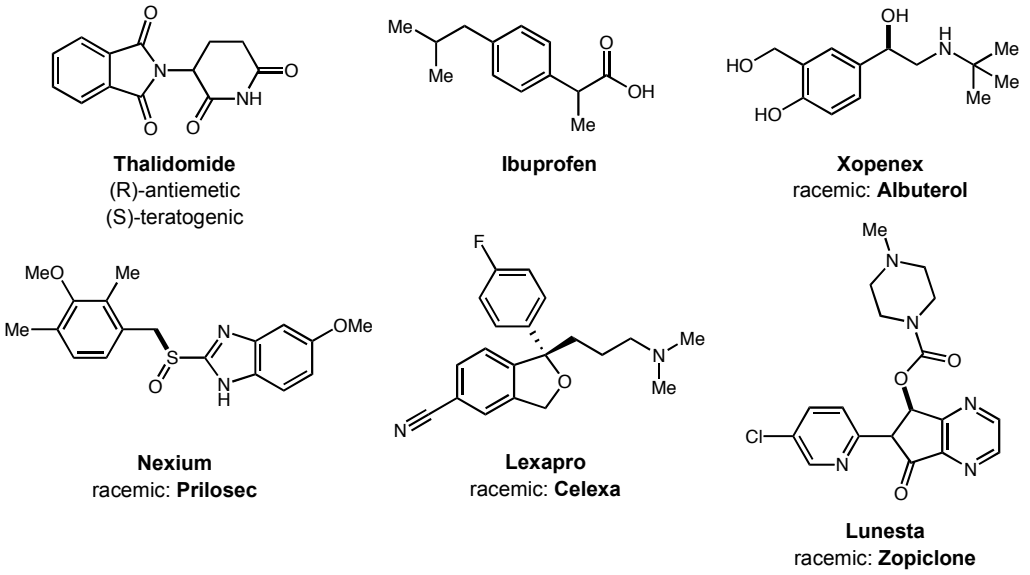

Figure 1. Pharmaceuticals marketed as racemic mixtures. Many were later marketed in the enantiopure form when generics of the racemic drug became available.

of birth defects.[3] It was later discovered that only the (S)-enantiomer of the drug is teratogenic. Since that time, numerous racemic drug formulations have been marketed worldwide. Due to required rigorous safety testing, drugs with toxic enantiomers like thalidomide no longer reach the consumer. However, many racemic formulations have been marketed in which one enantiomer is inactive, in essence doubling the minimum effective dose. History has shown that all pharmaceuticals have some degree of undesirable side effects, a risk that could be significantly reduced by removal of the unwanted enantiomer to provide a generally safer drug. For this reason, the development of new methods for inducing asymmetric transformations has been a focal point of extensive research in the chemical field over the last several decades.

[3] Bren, L. Frances Oldham Kelsey: FDA Medical Reviewer Leaves Her Mark on History. *FDA Consumer–U.S. Food and Drug Admin.* **2001**, *35*, *No. 2*.

Asymmetric Catalysis

Of the known methods for generating enantiomerically pure stereocenters from achiral starting materials, asymmetric catalysis is the most desirable for both cost and environmental reasons as a single chiral catalyst that is used in very small quantities can induce the production of large quantities of enantio-enriched material. Additionally, catalysts are often reusable, resulting in a significant reduction in the amount of waste produced during the process compared to a stoichiometric reaction. In order for an asymmetric catalyst to successfully induce chirality in the final desired product, the reaction rate of the uncatalyzed process must be significantly slower than the catalyzed reaction. To achieve this, a catalyst must sufficiently activate one or more of the chemical reagents, attaining essentially new reactivity.

Over the years, chemists have invented a plethora of asymmetric catalytic reactions, yet most have been generated using relatively few chemical activation modes, such as metal-insertion, atom transfer, and Lewis acid catalysis.[4] The importance of the discovery of these early activation modes on the field of chemical synthesis was demonstrated by the 2001 Nobel Prize in Chemistry being awarded to William S. Knowles, Ryoji Noyori, and K. Barry Sharpless for their "work on chirally catalyzed hydrogenation reactions" and "chirally catalyzed oxidation reactions."[5]

Until recently, the field of asymmetric catalysis was predominated by chiral transition metal catalysts. These metallic catalysts induce chirality via their enantiopure

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[4] (a) *Comprehensive Asymmetric Catalysis I–III*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Heidelberg, 1999. (b) *Asymmetric Catalysis in Organic Synthesis*; Noyori, R., Ed.; Wiley: New York, 1994. (c) *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000.

[5] (a) Knowles, W. S. *Angew. Chem. Int. Ed.* **2002**, *41*, 1998. (b) Noyori, R. *Angew. Chem. Int. Ed.* **2002**, *41*, 2008. (c) Sharpless, K. B. *Angew. Chem. Int. Ed.* **2002**, *41*, 2024.

ligands, which are often expensive and difficult to synthesize. The metals themselves are typically expensive and unstable to air and water in the atmosphere, which requires special handling and storage capabilities. In addition, these catalysts are often difficult to isolate for reuse and their toxicity makes them especially undesirable in pharmaceutical manufacturing processes. Luckily, these catalysts are typically highly efficient, such that only extremely small quantities are required for the synthesis of large amounts of desired material.

An alternative to metal catalysis that went almost completely unexplored until ten years ago is the field of organocatalysis, where the catalyst is itself an organic molecule. Organic molecules have the advantage of being insensitive to air and moisture, which makes handling them easier and the reactions performed with them more reproducible. The first organocatalyzed reaction was reported in 1912 by Bredig and Fiske, who found that cinchona alkaloids significantly accelerated the addition of HCN to benzaldehyde.[6] Since then, isolated examples of organocatalyzed reactions have been reported, but their general applicability to a wide range of organic transformations has only recently been realized. For example, in 1971 Eder, Sauer and Wiechert discovered that the amino acid L-proline is capable of catalyzing asymmetric intramolecular aldol reactions.[7] The reaction was not explored further for nearly thirty years, until Barbas et al. reported the proline-catalyzed intermolecular aldol condensation between ketones and aldehydes.[8] This sparked research efforts towards utilizing the enamine intermediate as an enolate

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[6] Bredig, G.; Fiske, W. S. *Biochem Z.* **1912**, 7.

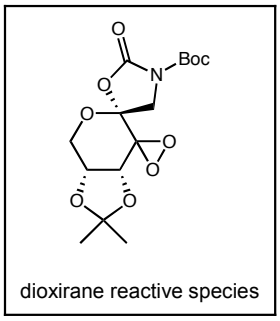
[7] (a) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem.* **1971**, *83*, 492; *Angew. Chem. Int. Ed.* **1971**, *10,* 496. (b) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615.

[8] List, B.; Lerner, R. A.; Barbas, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395.

surrogate, leading to many new asymmetric transformations, and the process became known as "enamine catalysis."

Organocatalytic Modes of Activation

In the last ten years, the field of organocatalysis has exploded from a few isolated reactions in the literature to a thriving new field of chemical research encompassing a broad range of useful reactions and unprecedented reactivities.[9] In many respects, organic catalysts have been able to accomplish many of the same reactions and emulate many of the modes of reagent activation as metal catalysts. More importantly, organic catalysts have also enabled new chemical reactivities that were historically unattainable with metal catalysts. For example, emulating the atom transfer capabilities of transition metal catalysts (Figure 2), the ketone-catalyzed epoxidation and aziridination reactions developed by Shi (equation 1),[10] Denmark,[11] and Yang[12] were among the first organocatalytic reactions to be widely used in organic synthesis community.



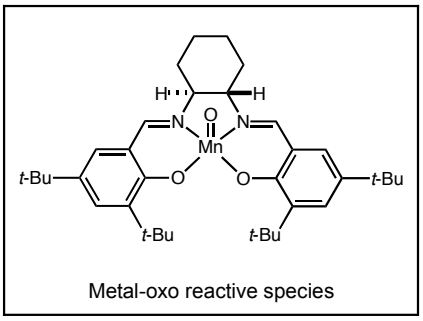


Figure 2. Reactive species of the atom transfer reactions catalyzed by Shi's chiral fructose-derived ketone catalyst and Jacobsen's manganese salen catalyst.

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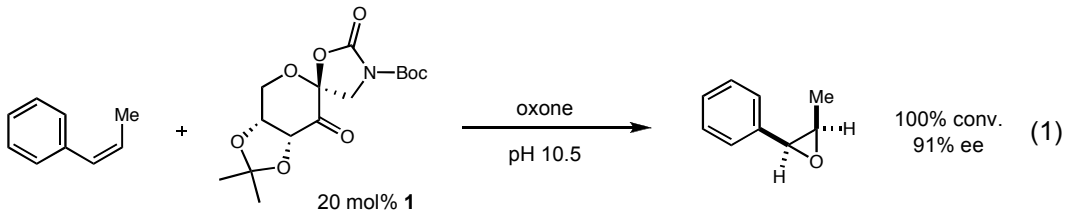
[9] *Asymmetric Organocatalysis*, Berkessel, A., Gröger, H., Eds.; Wiley-VCH: Weinheim, 2005.

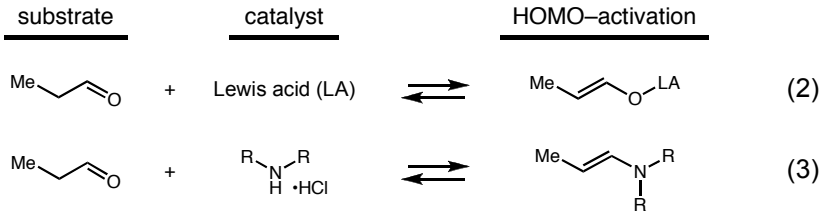
[10] (a) Tu, Y.; Wang, Z. X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806. (b) Tian, H. Q.; She, X. G.; Shu, L.-H.; Yu, H. W.; Shi, Y. *J. Am. Chem. Soc.* **2000**, *122*, 11551. (c) Hickey, M.; Goeddel, D.; Crane, Z.; Shi, Y. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5794.

[11] Denmark, S. E.; Wu, Z. C. *Synlett* **1999**, 847.

[12] Yang, D.; Wong, M. K.; Wang, X. C.; Tang, Y. C. *J. Am. Chem. Soc.* **1998**, *120*, 6611.



Likewise, the traditional Lewis acid-catalyzed highest occupied molecular orbital (HOMO)-raising activation of carbonyls to form nucleophilic metal enolates is successfully mimicked by the reversible condensation of a secondary amine with a ketone or aldehyde, which tautomerizes to form a nucleophilic enamine (equations 2 and 3). In addition to aldol reactions, this strategy has been successfully employed for many enantioselective transformations including Mannich-type reactions and α-heteroatom functionalization of ketones and aldehydes.[13]



Similar activation is achieved by ammonium enolates,[14] which can be formed via nucleophilic addition of a tertiary amine to ketenes, α,β-unsaturated carbonyls, and α-halogenated carbonyls (Figure 3a-c), or via deprotonation with an ammonium base as in phase-transfer catalyzed reactions (Figure 3d).[15] Addition of N-heterocyclic carbenes to aldehydes generates a nucleophile of umpolung reactivity, enabling nucleophilic additions to the carbonyl carbon and enabling reactions such as the catalytic asymmetric

[13] Mukerjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471.

[14] Gaunt, M. J.; Johansson, C. C. C. *Chem. Rev.* **2007**, *107*, 5596.

[15] Maruoka, K.; Ooi, T. *Angew. Chem. Int. Ed.* **2007**, *46*, 4222.

benzoin condensation and Stetter reaction (Figure 3e).[16] All of these HOMO-raising activation modes have now been applied to many different asymmetric transformations with great success.

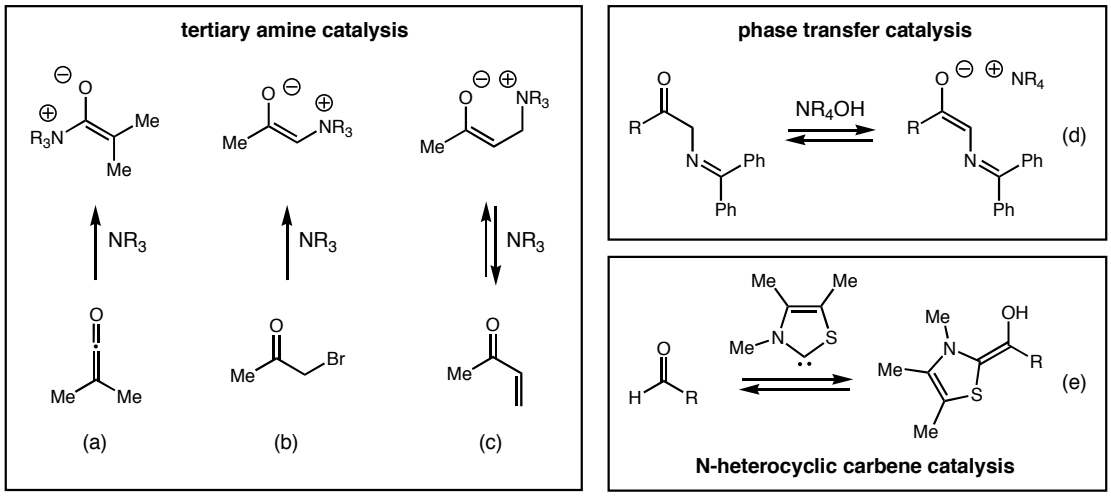
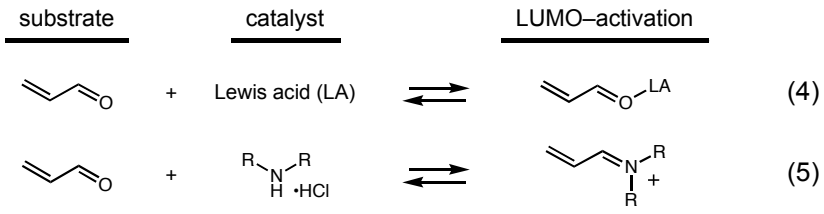


Figure 3. Organocatalytic modes of HOMO-raising activation.

In contrast to the HOMO-raising modes of activation that generate activated nucleophiles, our lab simultaneously envisioned emulating the Lewis acid activation of electrophiles via the reversible condensation of a secondary amine catalyst with α,β-unsaturated aldehydes and ketones to form activated iminium species (equations 4 and 5). This lowest unoccupied molecular orbital (LUMO)-lowering activation mode, termed "iminium catalysis," proved broadly useful for the invention of many new organocatalytic reactions such as cycloadditions, Friedel Crafts alkylations, and



[16] (a) Marion, N.; Díez-González, S.; Nolan, S. P. *Angew. Chem. Int. Ed.* **2007**, *46*, 2988. (b) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606.

heteroatom conjugate additions.[17] Various other forms of LUMO-lowering activation of electrophiles have now come to fruition, such as H-Bonding and Brønsted acid catalysis[18] in which coordination of a hydrogen atom enhances a reagent's electrophilicity, and Lewis base catalysis,[19] in which the catalyst binds to a silicon atom, causing it to become a strong Lewis acid (Figure 4).

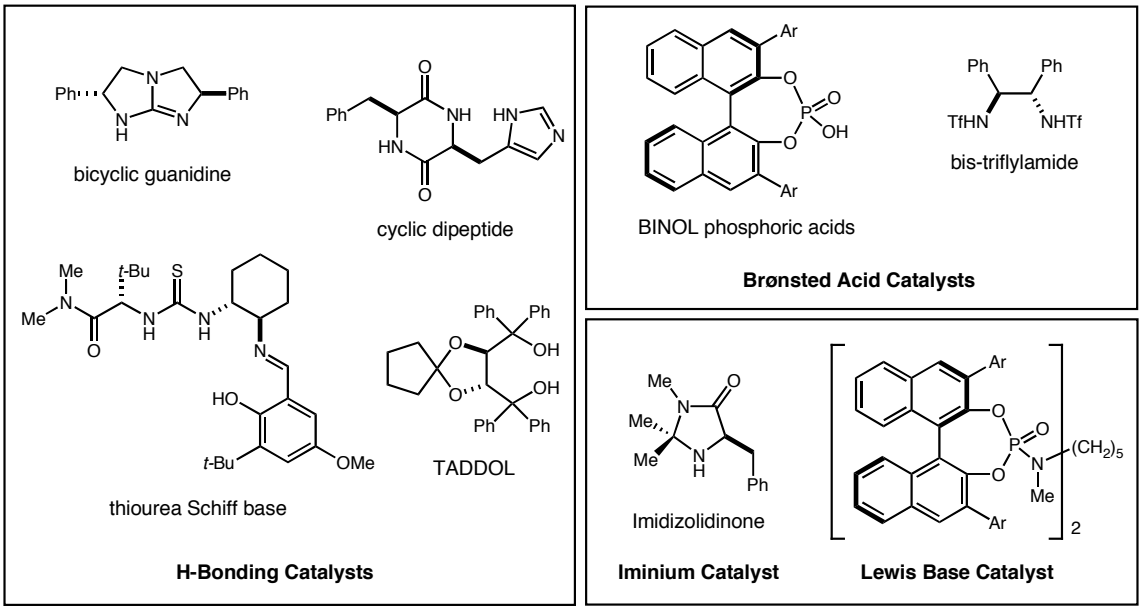


Figure 4. Organocatalysts used in LUMO-lowering activation of electrophiles.

Summary of Thesis Research

The following chapters describe applications of the HOMO-raising activation of enamine catalysis and the subsequent development of a new mode of organocatalytic activation, SOMO-catalysis. Chapter 2 discusses the development of a rapid and enantioselective one-pot conversion of aliphatic aldehydes to terminal epoxides using the

[17] Lelais, G.; MacMillan, D. W. C. *Aldrichimica Acta* **2006**, *39*, 79.

[18] Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713.

[19] Denmark, S. E.; Beutner, G. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 1560.

organocatalyzed α-chlorination of aldehydes as a chiral synthon intermediate. Chapter 3 details the development of the enantioselective α-fluorination of aldehydes using chiral imidizolidinone catalysts and electrophilic fluorinating agents. Chapter 4 reports advancements towards the asymmetric α-fluorination of ketones by the identification of a suitable catalyst class. Chapter 5 chronicles the invention of SOMO-catalysis, from concept to implementation, as a new mode of organocatalytic activation that enables an entirely new variety of catalytic asymmetric transformations and details the development of the enantioselective SOMO-catalyzed α-allylation of aldehydes as a proof of principle.